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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/881,976	06/15/2001	Matthias Rath	11957/2	8960

26646 7590 09/29/2003

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ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/29/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	Examiner	Group Art Unit	

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on the ~~the~~ RCE & amendment filed 8/8/03.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-11 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 1-11 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____ ☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892 ☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948 ☐ Other_____

Office Action Summary

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/8/03 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The rejection of claims 1-11 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention is maintained. The claim language has been amended but the thrust of the invention remains the same.

Applicant's previous arguments have been fully considered but are not deemed to be persuasive. Applicant argues that the claimed invention is directed to a method of producing a vaccine from a signal oligopeptide and that the specification provides a detailed disclosure to allow person of ordinary skill in the art to

recognize that the inventor had possession of the claims invention. Various portions of the specification are cited to bolster the argument that the inventor was in possession of the claimed invention. However, a review of the specification reveals that the specification discloses a list of sequences arrived at by data mining with only prophetic examples of use. There are no examples of producing vaccines as per the claims. It is noted that the description of figure 3 on page 7, line 18, is interesting in that there is a parenthetical statement "I don't have this". Also, the discussion of Figure 3 on page 16, 20, has a typographical error. Applicant asserts that the examiner subjectively places himself as "one of ordinary skilled [sic] in the art". This is not correct on two counts. First, the standard is "one skilled in the art", and second, the Office objectively ascertains the level skill and knowledge in the art. One skilled in the art at the time the invention was made would not recognize that a peptide having high hydrophilicity is equivalent to a vaccine. Based on this, it appears applicant has created a list of peptides with high hydrophilicity through a computer algorithm but was not in possession of any vaccines. Applicant argues that there are working examples but has only shown hypothetical, prophetic, examples. In view of the above, the specification lacks an adequate written description of the claimed invention.

The rejection of claims 1-11 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

Applicant argues that there is a detailed description of determining hydrophilicity and surface probability algorithms, PIT and argues that given the "current knowledge in antibody and vaccine" [sic], one would be able to make and use the invention by preparing a synthetic peptide based on the current understanding of a disease-causing protein, determine the area of maximum hydrophilicity, prepare a vaccine or antibody which fully enables the scope of the claims.

Applicant argues that the disclosed sequences are identified as being attributed to many human diseases and that Example 6 allegedly illustrates the use of peptides in lowering cholesterol in cells.

Applicant further cited *In re Wands* and concludes that the present case purportedly shares many factual findings with *Wands* such as antibody technology and process steps. Applicant submits that the instant case i) provides a detailed disclosure, ii) there is a high level of skill in the art, iii) there is good predictability in vaccine art, iv) the specification provides adequate

direction, v) the specification provides working examples, v) [sic, vi] algorithm and immunization procedures are merely routine.

Applicant goes on to note that the present application was filed 13 years after *Wands* and that knowledge and skill in the art has advanced and argues that it is illogical and irony [?] that the instant case can lack enablement. Apparently, applicant is arguing that, by virtue of being filed after *Wands*, it is not appropriate to make an enablement rejection.

Applicant argues that so long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims, the enablement requirement is met and has done so in the present case by the alleged presence of working examples that identifying a disease causing protein, synthesizing a signal protein after determining hydrophilicity and/or charge, and how to use the invention in therapeutic application. Applicant goes on to state that the present specification provides a detailed instruction of how to make and use the invention and is fully enabled for the scope of the claims.

Applicant's arguments have not been deemed to be persuasive. Initially, it is noted that applicant did not address the issues raised in the previous office action in regards to art recognized

issues concerning signal peptides, specifically Watanabe et al. and Hogh et al.

Applicant's point about one being able to make and use the invention by preparing a synthetic peptide based on the current understanding of a disease-causing protein, determining the area of maximum hydrophilicity, preparing a vaccine or antibody is not convincing. There are problems with this argument because applicant is arguing limitations that are not in the claims, specifically, the method is to identify a peptide associated with a disease, determine the area of hydrophilicity, and create a vaccine peptide. Further, there is nothing in the claims about antibodies. There is nothing in the art that demonstrates that peptides with regions of high hydrophilicity are vaccines to prevent disease and the specification only provides prophetic examples with no actual results.

In regards to the discussion about Example 6, this is not understood. There is no Example 6 and there are no examples that actually demonstrate treating any disease beyond hypothetical scenarios in prophetic examples.

Applicant's discussion about *In re Wands* is not persuasive. The mere presence of antibody or process steps hardly puts any given invention within the reach of *Wands*. Further, there are no claims to antibodies, let alone, hybridomas, so it is not clear how

this point relates to the instant application. Applicant's assertion that the instant disclosure meets the criteria of the *Wands* factors is not agreed to by the examiner. Applicant's point (i) [detailed disclosure] is not on point and is inaccurate. As a matter of fact, applicant has rearranged the usual order of the *Forman* factors as restated in *Wands*. As the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Taking these factors in order as they relate to the instant invention, (1) the quantity of experimentation is high, (2) the amount of direction or guidance is minimal, consisting only of prophetic examples, (3) the specification lacks any working examples and is based solely on speculation, (4) the nature of the invention is a method for producing vaccines to any disease, (5) the state of the prior art is such that methods of producing vaccines to a few contagious diseases are known, (6) the relative skill of those in the vaccine art is high, (7) the art is highly unpredictable, and (8) the breadth of the claims are very broad in that the method is asserted to be applicable to incredibly wide

array of divergent diseases with no common features underlying their pathologies.

To further expand upon these points, the instant invention is drawn to a method of producing vaccine compositions comprising a peptide with high hydrophilicity but the specification does not sufficiently support the full scope of the claimed invention, specifically, the resultant vaccine. The term "vaccine", by definition, implies a preparation intended for active immunological prophylaxis; e.g., preparations of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains; or microbial, fungal, plant, protozoa, or metazoan derivatives or products. Although nearly any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. For example, the *Illustrated Dictionary of Immunology* defines vaccine as a composition that stimulates protective antibodies and T cell immunity and induces active immunity. Paul in *Fundamental Immunology* teaches that vaccines were developed primarily as a prophylactic measure to prevent disease. This is achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members of a community

to reduce the number of carriers of a disease and to prevent others from contracting the disease. Testing protocols are designed to test the efficacy of the vaccines which include challenge trials or natural exposure to the disease agent in an endemic area. Further, he teaches that there is not always a correlation between sero-conversion and protection from disease. Given the teachings in the art, it is clear that a compound that merely induces an immune response is not sufficient but must be protective to qualify as a vaccine. See at the top of page 1312: "[T]here was not always a correlation between seroconversion and protection from disease...."

The ability of a vaccine to raise a protective immune response depends on the structure of the protein epitopes. Paul teaches that to determine the immunogenicity of certain regions of a protein, knowledge of the three dimensional structure of the protein is required. In addition, Paul states that mobility of the putative antigenic determinant within the native protein structure is also a determining factor for the binding of the antigenic determinant to an antibody. Paul points out (page 250, lines 4-8) that "Measurement of the mobility in the native protein is largely dependent on the availability of a high resolution crystal structure, so its applicability is limited to only a small subset of proteins." Riffkin et al. (*Gene*, 1995) teaches that a single amino acid change can alter the structure of the protein dramati-

cally. Abaza et al. (*J. of Protein Chemistry*, 1992) teaches that mutations outside of the antigenic epitope exert an effect on the structure of the epitope. Because the structure of the protein determines it antigenicity and thereby its function as a vaccine, these structures cannot be predicted.

To take just one embodiment that falls within the scope of the claims, the production of an anti-HIV vaccine, much work has been done and success is still elusive. The difficulties inherent to development of an HIV vaccine are well known. Specifically:

1) the extensive genomic diversity associated with the HIV retrovirus, due in large part to error prone reverse transcription of its single-stranded RNA genome, i.e., high mutation rate,

2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert form (cell to cell transmission), as well as via free virus transmission,

3) the existence of latent forms of the virus (i.e., beyond the blood-brain barrier),

5) the complexity and variation of the elaboration of the disease and,

6) the property of some portions of HIV proteins or peptides to actually cause immunosuppression or other detrimental consequences.

Though these difficulties are known and recognized in the art, the instant specification has not provided any teachings that show how, or even if, the claimed invention has overcome them. Even being aware of the problems in the development of an HIV vaccine and the many proteins associated with the virus, there is, according to Cohen et al. (PNAS, 1999), "No vaccine capable of eliciting protective immunity to HIV infection has been formulated. HIV presents a formidable challenge to immune surveillance based on many factors, including hypervariability of its principal neutralizing domain (V3), concealment of critical, functional domains in the external envelope glycoprotein (gp120) behind inessential structures, and infection of APCs resulting in their dysfunction. Substantial progress has been made recently in defining neutralizing domains within the HIV envelope, and in augmenting the immune response to HIV proteins. Despite these important advances, an effective HIV vaccine remains elusive, we propose, because the immediate immunodeficiency accompanying HIV infection creates another obstacle to a successful vaccine."

The lack of success can be cited in many other diseases as well owing to problems particular to each disease. Not to put too fine a point on it, one can also look at cancer and recall that the government's "War on Cancer" has been waged for many years and there is yet to be a vaccine for cancer. In regards to the factors

cited above, applicant's specification does not address these factors and does not disclose that the instant invention has overcome these problems.

Though vaccines for a relative few contagious diseases are known, the development of vaccines for each specific organism or disease is fraught with uncertainty. If it were not, there would not be any incurable or unavoidable diseases as vaccines would be relatively easy to produce. Heretofore, nobody has produced a widely applicable formula for doing so although it would certainly be very desirable. Therefore, the specification is an invitation to the artisan to experiment with the 360 peptides disclosed to see if any of them are vaccines. The instant specification is not enabled for the claimed invention and provides no examples commensurate in the scope of the claims, it only teaches selecting peptides with high degree of hydrophilicity. There are prophetic examples but no evidence that any peptide with a high degree of hydrophilicity will be suitable for a protective vaccine. There is no teaching in the art that demonstrates that such peptides are functional as vaccines to prevent disease nor is there any guidance in the art to this affect to make up for the deficiencies of the specification.

Given the uncertainty in the vaccine art as demonstrated by the references and the lack of working examples in the instant

specification, the instant application is not enabled for methods of producing vaccines.

The rejection of claims 1-11 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is withdrawn** in view of the amendment to the claims.

The following is a new ground of rejection necessitated by applicant's amendment:

Claims 1-11 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by "treating a disease" which contradicts "vaccine" which implies preventing which would not allow a disease to occur, obviating the need for treatment.

It is not clear if a "peptide having the amino acids sequence" is opened or closed language.

Claims 1 and 10 are objected to for a minor typographical error: In line 3 after "treating a disease in" there should be inserted "a".

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the

advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

The Group 1600 Fax number is: (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Stucker whose telephone number is (703) 308-4237. The examiner can normally be reached Monday to Thursday from 7:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeffrey Stucker

JEFFREY STUCKER
PRIMARY EXAMINER